NIMH
National Institute of Mental Health

NATIONAL INSTITUTE OF MENTAL HEALTH, NIH
REQUEST FOR PROPOSAL - SOLICITATION COVER PAGE

REQUEST FOR PROPOSAL NO:	NIMH-02-DB-0005 **AMENDMENT 01**
TITLE:	*NIMH Program for Toxicological Evaluation of Novel Ligands*
OMB No.: 0990-0115	**PURCHASE AUTHORITY:** Public Law 92-218 as amended; Note: The issuance of this solicitation does not commit the Government to make an award, or to pay any costs for the preparation and submission of a proposal.
ISSUED BY: Bruce E. Anderson Contracting Officer Contracts Management Branch National Institute of Mental Health, NIH Neuroscience Center Building 6001 Executive Blvd., Rm. 6107 (MSC 9603) Bethesda, MD 20892-9603 **POINT OF CONTACT:** Bruce E. Anderson E-mail: ba9i@nih.gov Phone (301) 443-2696 or 2234 Fax at (301) 443-0501 Collect calls will not be accepted.	**ISSUE DATE:** February 22, 2002 **DUE DATE: May 14, 2002 - CHANGED** **4:00 p.m., local prevailing time** Note: The official Point of Receipt for the purposes of determining timely delivery is the Contract Management Branch, NIMH. A paper copy with original signatures is the official copy for recording timely receipt. If the Contracting Officer or Designee does not receive your proposal at the place and time specified, then it will be considered late and handled in accordance with PHS Clause 352.215-10 entitled "Late Proposals, Modifications of Proposals and Withdrawals of Proposals" located in this solicitation. Facsimile submissions are not acceptable.
NO. OF AWARDS: **PERIOD OF PERFORMANCE:**	One (1) Three (3) years, beginning on or about September 30, 2002, with two (2) one-year options to extend (total 5 years)
SMALL BUSINESS/ 8(a) SET-ASIDE:	No, NAICS Code 541710 Size Standard: 500 employees
JUST IN TIME:	Yes
OFFER EXPIRATION DATE:	Offers will be valid for 120 days unless a different period is specified by the Offeror on the form entitled "Proposal Summary and Data Record, NIH-2043" (See Attachment 4)
TECHNICAL PROPOSAL PAGE LIMITS: **AWARD WITHOUT DISCUSSIONS:**	No The Government anticipates making an award after conducting negotiations, but reserves the right to make an award without discussions

NOTE: OFFERORS ARE RESPONSIBLE FOR ROUTINELY CHECKING THE NIMH WEBSITE AT http://www.nimh.nih.gov/grants/indexcon.cfm FOR ANY POSSIBLE SOLICITATION AMENDMENTS THAT MAY BE ISSUED. THIS OFFICE WILL PROVIDE NO ADDITIONAL NOTIFICATION OF ANY AMENDMENTS.

TO ALL OFFERORS: The purpose of this amendment is to change (extend) the due date for submission of proposals from April 23, 2002 to May 14, 2002. The amendment also provides clarifying information to the Statement of Work in the form of questions and answers (below). No other changes are hereby made to the solicitation.

Questions Received Regarding the Solicitation

Q1. On the "Estimated Cost Per Assay Chart" on page 68 of the RFP, you ask for separate costs for testing 1 compound in "Assay 5" and "Assay 6." Assay 5 describes a very broad range of studies (7-90 day treatments, multiple organ systems). Assay 6 includes both a broad list of genetic toxicology batteries and teratology studies (animal species not specified). A single price for each assay cannot be provided on these without further information. Please clarify.

A1. The estimated costs for Assay 5 should be based on a 30 day study for a CNS compound in which acute toxicity, safety pharmacology, toxicokinetics, and analytical chemistry testing data are available. The cost estimate should include protocol development and 30 day repeat dose toxicology, safety pharmacology, and toxicokinetic studies based on FDA Regulatory Pharmacology and Toxicology Guidance [http://www.fda.gov/cder/PharmTox/guidances.htm].

The estimated costs for Assay 6 should be based on protocol development for genotoxicity studies and reproductive toxicity studies for a CNS compounds in which 30 day repeat dose toxicity, safety pharmacology, toxicokinetics, and analytical chemistry testing data are available. The cost estimate should include protocol development and the appropriate genotoxicity and reproductive toxicity studies based on FDA Regulatory Pharmacology and Toxicology Guidance [http://www.fda.gov/cder/PharmTox/guidances.htm].

Q2. For Assays 2 and 4, should prices include the cost of conducting plasma analyses? If so, will an analytical method be provided or should method development be included in the price?

A2. Yes, the price estimate should include the cost of conducting plasma analyses and methods development listed as separate line items for Assays 2 and 4.

Q3. Should analytical chemistry evaluations of dose solutions required by GLP regulations be included in the costs of each study? If so, stability and homogeneity testing are generally only conducted once; should the cost of these analyses be included in the rat acute toxicity studies, as these are generally the first studies to be conducted? Should method development costs also be included, or will an analytical method be provided?

A3. Yes, analytical chemistry evaluations of dose solutions should be included in the costs of each study. Stability and homogeneity testing should be included in the rat acute toxicity studies. Method development should be included in the estimate, listed as a separate line item.

Q4. For all Assays (but especially Assay 4), you list specific protocol requirements, and then state that studies should be conducted "as specified by FDA/ICH guidelines." In several cases, your requested protocol would not comply with ICH requirements (e.g., ophthalmology, urinalysis, gross necropsy, organ weights are required for repeat-dose IND-directed studies under ICH guidelines, but are not requested in your protocols). Should we provide prices on the protocol outlines you have provided or on more typical ICH protocols, which would generally be more expensive?

A4. The protocol detailed in the RFP serves as a starting point for the offeror to identify the appropriate tests needed to obtain an IND for CNS imaging ligands (PET, SPECT, fMRI) or, in some cases, CNS compounds that will be used as pharmacologic probes in clinical research studies (assume the compounds are novel chemical entities rather than modifications of FDA approved drugs). The most appropriate guidelines for the protocol development for CNS imaging ligands (Assays 1-3) are the FDA Guidance for Industry: Developing Medical Imaging Drugs and Biological Products [http://www.fda.gov/cder/guidance/3646dft.htm]. The most appropriate guidelines for protocol development for CNS compounds that are being developed for chronic use as probes in clinical research or as potential therapeutics (Assays 4-6) are the FDA Regulatory Pharmacology and Toxicology Guidance that cites ICH Guidelines [http://www.fda.gov/cder/PharmTox/guidances.htm].

Q5. In Assay 1, should the cost of performing the functional observational battery (FOB) be included in the rat study?

A5. Yes, the cost of performing the FOB should be indicated as a line item for Assay 1.

Q6. In Assay 1, you state, "Necropsy shall be done in control and high dose groups first to identify organs showing toxicity." Target organs will not be determined until histopathology is complete. Is it correct to assume you mean that all animals will be necropsied as scheduled, but only histology slides will be prepared from target organs in mid- and low-dose groups?

A6. Necropsy should be conducted according to the FDA Guidance for Industry: Developing Medical Imaging Drugs and Biological Products [http://www.fda.gov/cder/guidance/3646dft.htm]. Any organs with macroscopic findings in high, mid, or low dose groups should be preserved for possible histological evaluation along with corresponding organs from the control group. If there are no findings at necropsy, a minimum of 13 appropriate organs should be selected for histological evaluation.

Q7. In Assay 1, you state, "Termination points for experimental measures: (possibly 1), 3, and 14 days..." Should the price include the additional (Day 1) interim sacrifice, or only the 3 and 14 day sacrifice groups?

A7. Yes, the price in Assay 1 should include the day 1 sacrifice group.